Exploring Newer Treatment Options in ANCA-Associated Vasculitis to Address Management Gaps

April 13, 2022

Faculty Information

Abigail Jastrab, PharmD, BCPS

Senior Manager, Clinical Systems

PANTHERx Rare Pharmacy

Pittsburgh, Pennsylvania

Faculty and Staff Disclosures

Abigail Jastrab, PharmD, BCPS, has no relevant financial relationships with commercial interests to disclose.

Pharmacy Times **Continuing Education™ Planning Staff:** Jim Palatine, RPh, MBA; Maryjo Dixon, RPh, MBA; Karleen Melody PharmD; Abigail Dill; Susan Pordon; Chloe Taccetta; and Brianna Winters have no financial relationships with commercial interests to disclose.

An anonymous peer reviewer has been used as part of content validation and conflict resolution. The peer reviewer has no relevant financial relationships with commercial interests to disclose.

The content of this activity may include information regarding the use of products that may be inconsistent with, or outside the approved labeling for, these products in the United States. Pharmacists should note that the use of these products outside current approved labeling is considered experimental and are advised to consult the prescribing information for these products.

Pharmacy Accreditation

Pharmacy Times Continuing Education™ is accredited by the Accreditation Council for Pharmacy Education (ACPE) as a provider of continuing pharmacy education.

This activity is approved for 1.0 contact hour (0.10 CEU) under the ACPE universal activity number 0290-0000-20-xxx-xxx-P.

Release Date: April 13, 2022

Activity Type: Application

Fee: Free

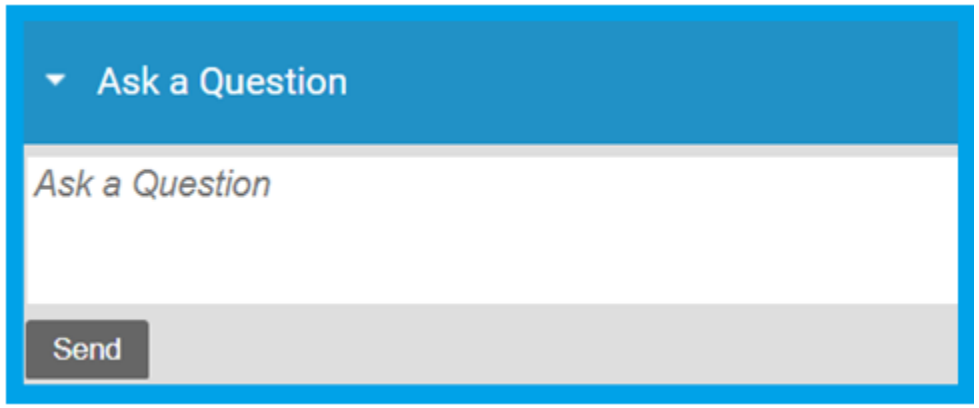
How to Obtain Credit

Instructions on how to obtain credit for this activity will be provided at the end of this presentation.

This activity is supported by an educational grant from ChemoCentryx.

Using GlobalMeet for Handouts and Q&A

To access a copy of the slides, click on Event Resources.



To submit a question for the Q&A session, enter your question within this box and click, “Send.”

Educational Objectives

After completion of this activity, participants will be able to:

- Explore the clinical presentation, challenges, and clinical burden of disease in patients with antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV)
- Identify the current challenges associated with treatment of AAV and the role of new and emerging therapies to address these treatment gaps
- Examine the role of pharmacists in providing patient education and recommendations in treatment strategies to improve outcomes in AAV

Pretest Questions

Pretest Question 1

Which of the following is true regarding antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV)?

A. A positive ANCA test is conclusive for an AAV diagnosis

B. The risk of relapse is 30% to 50% over 5 years with treatment

C. Acute renal injury is a common clinical presentation for all AAV subtypes

D. Purpura and weight gain have the largest negative impact on quality of life

Pretest Question 2

SM is a 55-year-old man with severe active granulomatosis with polyangiitis. SM struggles with uncontrolled hypertension, hyperglycemia, and other symptoms deemed related to his high prednisone doses. His physician recently tapered his prednisone to gain better control of SM's symptoms, but the taper resulted in this current flare. SM's physician is restarting induction therapy with rituximab (previous induction therapy with cyclophosphamide) and prednisone 60 mg orally daily. The pharmacist is asked to optimize his regimen to be able to reduce his prednisone dose.

A. Change rituximab to cyclophosphamide
B. Retry the steroid taper
C. Add avacopan
D. Add methotrexate

Pretest Question 3

JC is newly diagnosed with microscopic polyangiitis AAV, and the pharmacist is filling her first prescription for avacopan. Which counseling point should the pharmacist cover with JC, as it pertains to avacopan?

A. Signs and symptoms of stroke

B. Infertility

C. Significant drug interaction with prednisone

D. Signs and symptoms of hypersensitivity

Pretest Question 4

Before participating in this activity, how confident are you with new treatment options for AAV?

A. Not at all
B. Somewhat
C. Moderately
D. Very
E. Extremely

Overview of Antineutrophil Cytoplasmic Antibody-Associated Vasculitis

Abigail Jastrab, PharmD, BCPS

Background

AAV

Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV)

Overview

Autoimmune disorder that is comprised of a group of rare diseases that **cause inflammation** and **systemic necrotizing within small blood vessels**

Subtypes

- Granulomatosis with polyangiitis (GPA – aka "Wegener's granulomatosis")
- Microscopic polyangiitis (MPA)
- Eosinophilic granulomatosis with polyangiitis (EGPA – aka "Churg-Strauss syndrome")

Implications

Small blood vessel inflammation and damage can result in organ damage and failure

Prognosis

- Untreated and severe AAV can be fatal
- Current therapeutic regimens have significantly improved this prognosis

Chung SA, et al. *Arthritis Care Res (Hoboken).* 2021;73(8):1088-1105; Houben E, et al. *Medicine (Baltimore)*. 2016;95(40):e5096.

Epidemiology

Prevalence

Estimates range between 30 to 218/million; but increasing over time due to ↑ incidence and survival

GPA: 218/million

MPA: 184/million

EGPA: 18/million

Incidence

3.3 cases per 100,000 adults every year

GPA: 13/million

MPA 16/million

EGPA 4/million

Mortality rate

38.4/1000 person-years

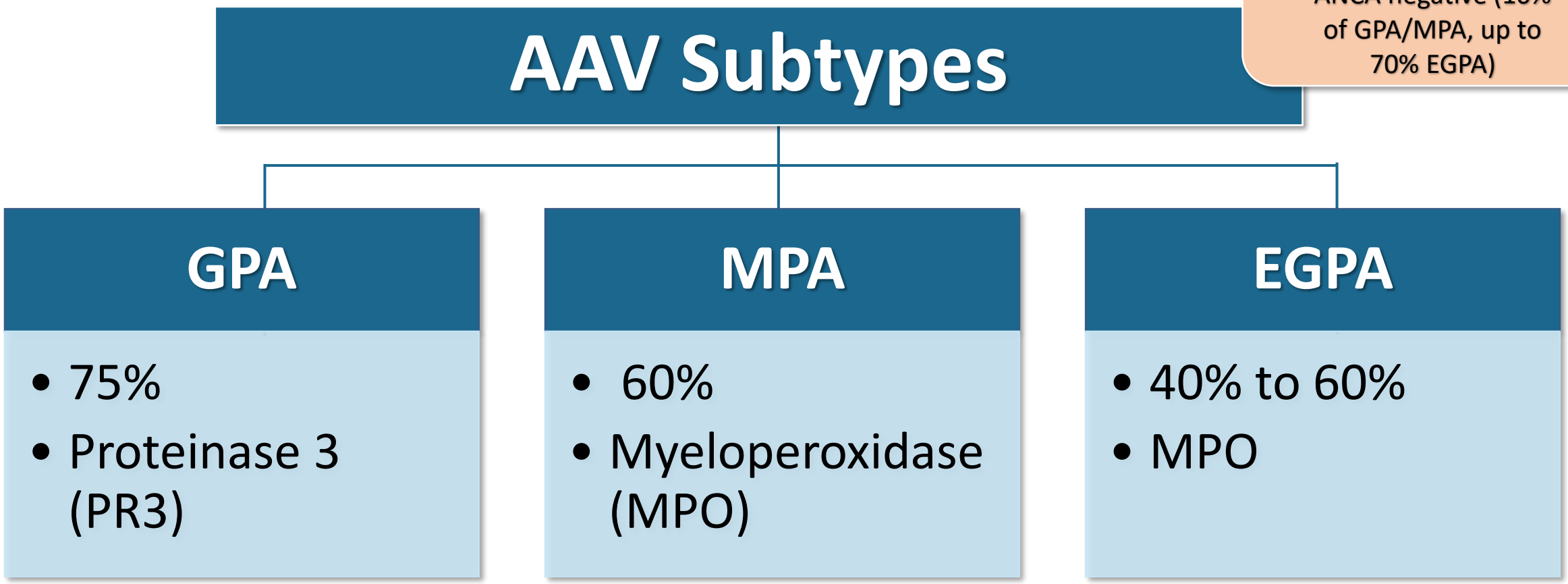
2.63-fold increase in mortality among those with GPA relative to the general population

Cause of death

Most common cause of death in AAV: cardiovascular disease, malignancy, and infection

Mohammad AJ. *Rheumatology (Oxford).* 2020;59(Suppl 3):iii42-iii50; Tan JA, et al. *Ann Rheum Dis*. 2017;76(9):1566-1574; Wallace ZS, et al. *Rheumatol*ogy (Oxford). 2020.;59(9):2308-2315; Berti A, et al. 2017 ACR/ARHP Annual Meeting. Poster Publication September 18, 2017.

Subtypes of AAV

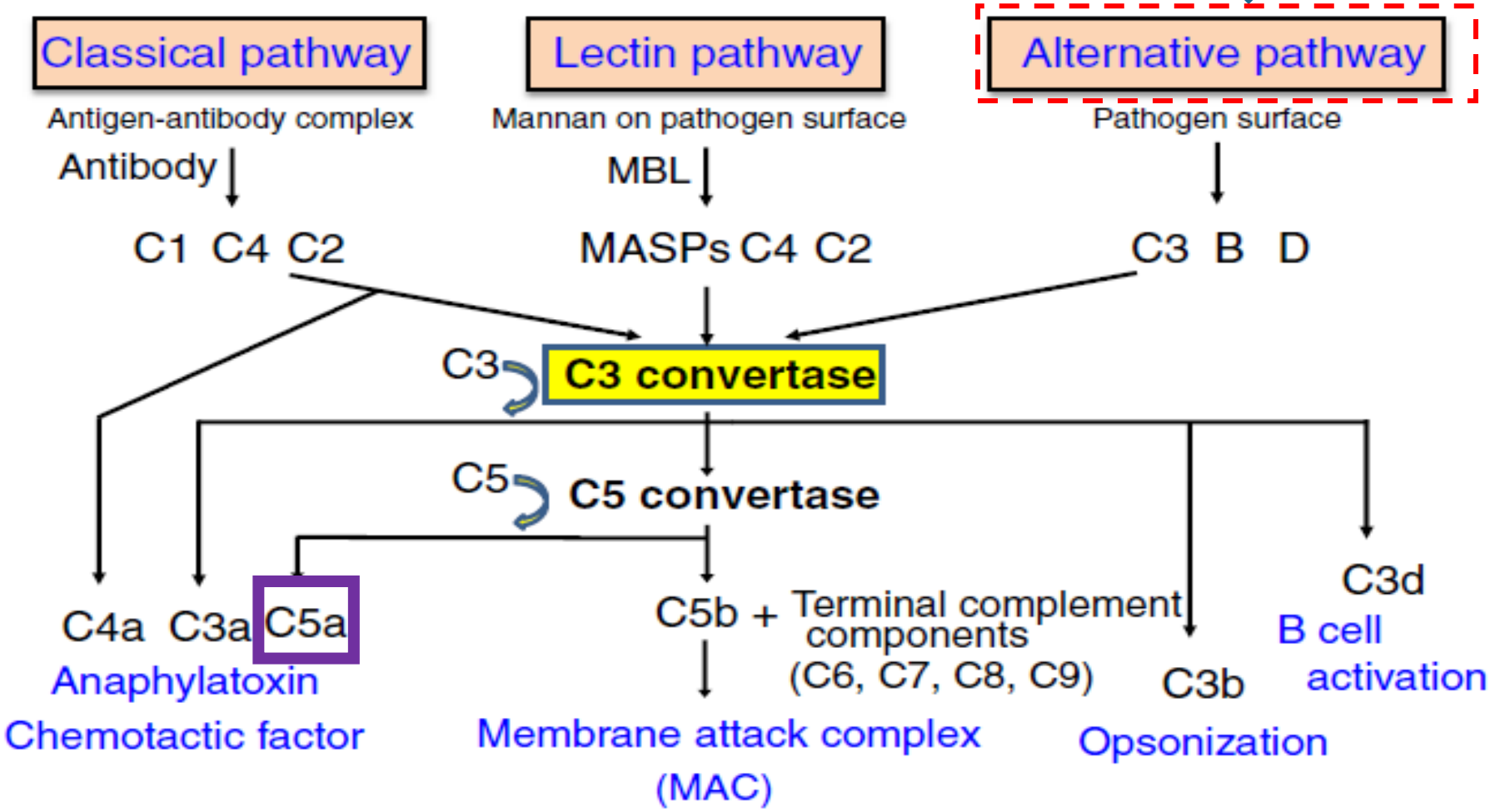


Any subtype can present as ANCA negative (10% of GPA/MPA, up to 70% EGPA)

Gioffredi A, et al. *Front Immunol.* 2014;5:549; Houben E, et al. *Medicine (Baltimore)*. 2016;95(40):e5096; Geetha D, Jefferson JA. *Am J Kidney Dis*. 2020;75(1):124-137.

Complement System

AAV



Neutrophil Priming and Activation

AAV **CANNOT** occur if PR3 and MPO remain within the cytoplasm

- Inflammatory cytokines trigger the neutrophil to become primed by moving MPO and PR3 to the neutrophil surface

What **triggers** AAV to occur in an individual?

- The pathogenesis is multifactorial
  - Genetics
  - Bacterial or viral infection (eg, *Staphylococcus aureus*)
  - Environmental factors (eg, silica, pesticides)
  - Medications associated with small-vessel vasculitis (eg, hydralazine, propylthiouracil, minocycline, anti-tumor necrosis factor agents)

Geetha D, Jefferson JA. *Am J Kidney Dis*. 2020;75(1):124-137.

Neutrophil Priming and Activation

1. Loss of tolerance to antigen: MPO or PR3

Silica

infection

Genetic Factors

environmental

DC

2. Autoimmunity to antigen develops

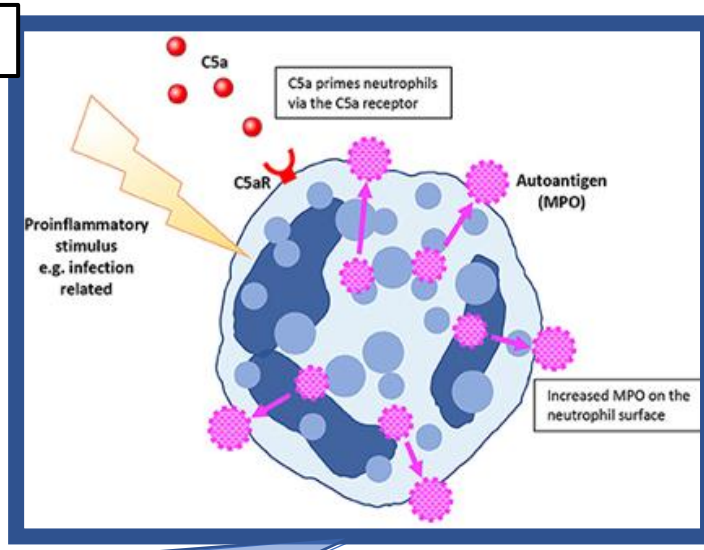
CD4

B

P

Alternative complement Activation produces C5a

ANCA



3. Neutrophil priming

4. ANCA binds to surface MPO/PR3

5. MPO/PR3 deposited on endothelium

Autoreactive T cells recognise MPO

Monocyte

Degranulation

NETosis

Diapedesis

Macrophage

6. Endothelial damage & inflammation resulting in vasculitis

MPO

TNFα

NE

ROS

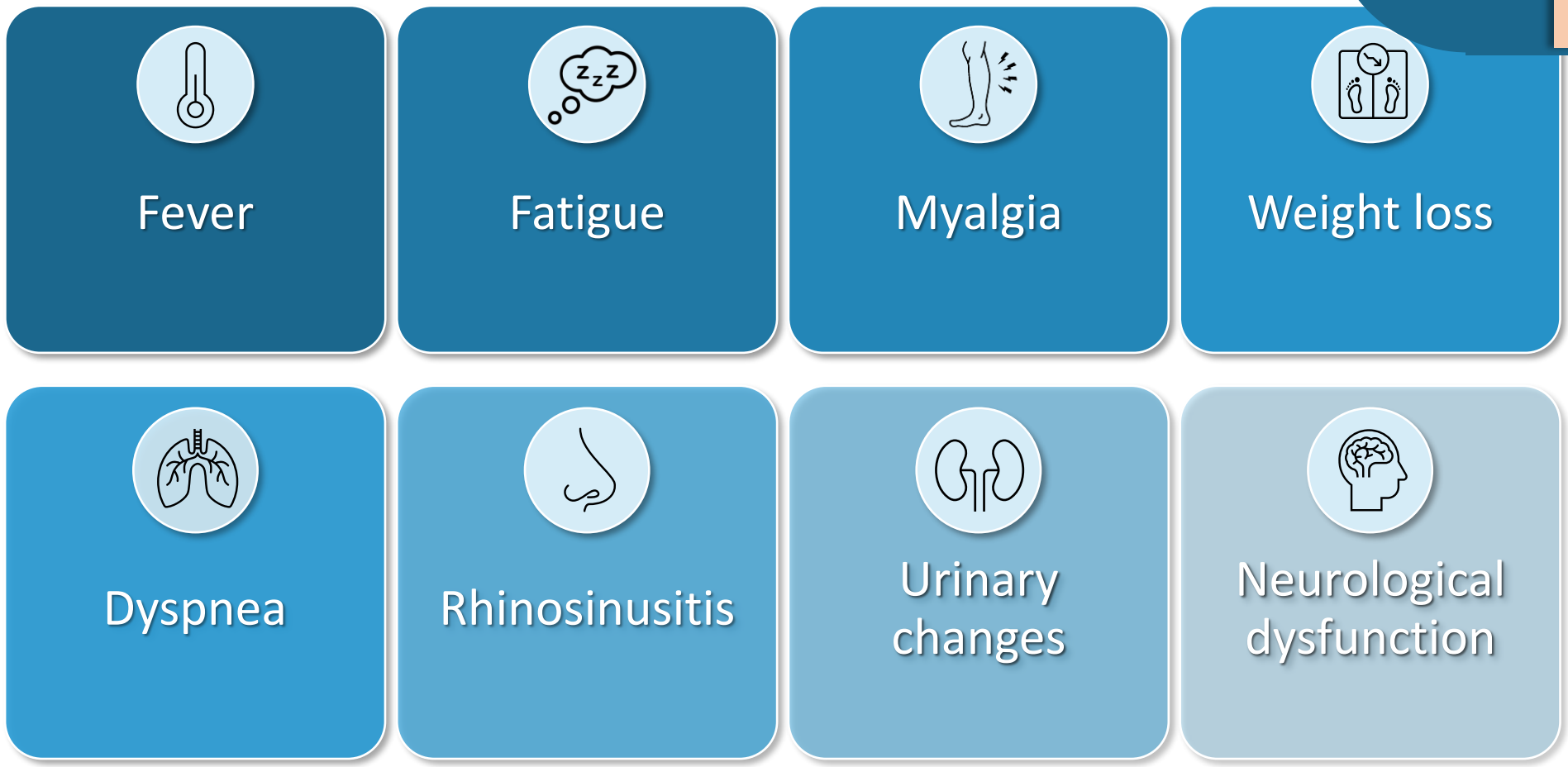
PR3

DNA

ANCA

General Clinical Presentation

Constitutional symptoms may present for months before AAV presentation



Salvador F. *Eur J Intern Med*. 2020;74:18-28.

Clinical Presentation: AAV subtype

GPA	• Pulmonary necrotizing granulomatous lesions (including cavitary nodules); acute renal injury; ear, nose, and throat (ENT) symptoms (eg, sinusitis)
MPA	• Chronic renal injury (eg, glomerulosclerosis), neuropathy, and rash
EGPA	• Asthma, peripheral eosinophilia, purpura, cardiomyopathy, gastrointestinal involvement, peripheral neuropathy, ENT symptoms (eg, allergic rhinitis)

Geetha D, Jefferson JA. *Am J Kidney Dis*. 2020;75(1):124-137; Yates M, Watts R. *Clinical Medicine*. 2017;17(1):60-64; Gioffredi A, et al. *Front Immunol.* 2014;5:549.

Burden of Disease

Impact on patient quality of life (QOL)

- One-third of patients present with **irreversible** damage at diagnosis
- **Fatigue** and **pain** have the largest negative impact on QOL
- 25% will suffer from **depression** and more than 40% present with **anxiety**
- 90% describe difficulties with ↓ levels of physical function

Mortality

- Despite treatment, the risk of relapse is 30% to 50% over 5 years
- Kidney disease is the most important predictor of mortality
- 1-year mortality in AAV has been >15%

Cazzador D, et al. *J Clin Rheumatol.* 2022;28(1):e89-e94; Robson JC, et al. *Patient Relat Outcome Meas*. 2018;9:17-32; Geetha D, Jefferson JA. *Am J Kidney Dis*. 2020;75(1):124-137; Terrier B, et al. *Ann Rheum Dis*. 2018;77:1150-1156; Koutantji M, et al. *Arthritis Rheum*. 2003;49:826-837; Flossmann O, et al. *Ann Rheum Dis.* 2011;70(3):488-494.

Burden of Disease

Costs and economic challenges

- ~25% unemployed
- Mean GPA-related health care costs were $24,319 during a 12-month follow-up
  - 18% of GPA: major relapse-related condition prior to first GPA diagnosis
  - Higher all-cause costs incurred vs those without a relapse
- MPA diagnosis: All-cause health care costs doubled ($30,166 vs $56,642)
  - 60.5% of MPA: major relapse-related condition prior to first MPA diagnosis

Cazzador D, et al. *J Clin Rheumatol.* 2022;28(1):e89-e94; Raimundo K, et al. *J Rheumatol.* 2015;42(12):2383-2391; Basu N, et al. *Rheumatology (Oxford).* 2014;53:953-956.

AAV Diagnosis

Positive ANCA serology cannot be used alone in the diagnosis of AAV

Other conditions presenting with increased ANCA

Inflammatory bowel disease

- Ulcerative colitis

Drug-induced AAV

- Hydralazine
- Propylthiouracil
- Minocycline
- Anti-tumor necrosis factor agents

Chronic infections

- Endocarditis
- Tuberculosis
- HIV
- Hepatitis

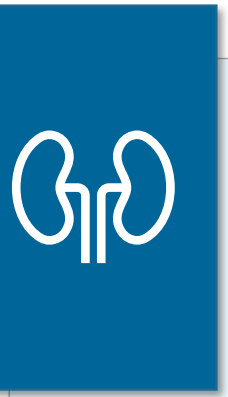
Other AAV-related conditions

- Primary pauci-immune necrotizing crescentic glomerulonephritis

Geetha D, Jefferson JA. *Am J Kidney Dis*. 2020;75(1):124-137.

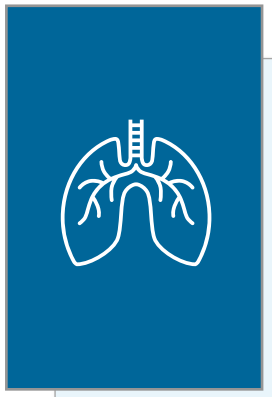
AAV Diagnosis

AAV diagnosis peaks in the 30's to 40's and again in the 70's to 80's



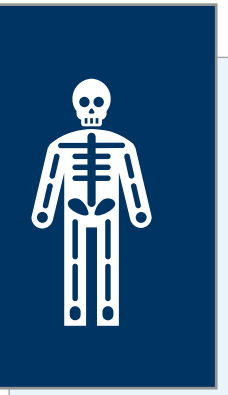
Biopsy

- Kidney biopsy most common site
- Can confirm AAV diagnosis



EGPA diagnosis

- Lanham diagnostic criteria (1984)
  - Asthma, plus either eosinophilia >1500/mm3 or >10% total white blood cell and evidence of vasculitis involving ≥2 organs



Clinical features

ANCA serology

- ANCA levels ≥4x upper limit of normal: 83.5% sensitivity, 78.6% specificity
  - ELISA → identifies PR3- vs MPO-ANCA (presence of both suggests drug-induced AAV)

Houben E, et al. *Medicine (Baltimore)*. 2016;95(40):e5096; Almeida S. et al. *Vessel Plus.* 2021;5:44; Gioffredi A, et al. *Front Immunol.* 2014;5:549.

Treatment Approaches and Advancements

Abigail Jastrab, PharmD, BCPS

Assessing Disease Activity

BVAS*			
Birmingham	**V**asculitis	**A**ctivity	**S**core

*56 item assessment

- All items determined as: **new/worse** or **persistent disease**
- If “new/worse” → disease manifestations recorded if active within past 4 weeks
- Ability to differentiate between:
  - Vasculitis and other conditions
  - Active disease from damage
  - Active disease, persistent disease, and remission

Mukhtyar C, et al. *Ann Rheum Dis.* 2009;68(12):1827-1832.

Assessing Disease Activity

Term	Definition
Active disease	New, persistent, or worsening clinical signs/symptoms of AAV that is not related to previous damage
Severe disease	Vasculitis with life- or organ-threatening symptoms (eg, alveolar hemorrhage, glomerulonephritis, central nervous system vasculitis, etc.)
Non-severe disease	Vasculitis without those life- or organ-threatening symptoms (eg, rhinosinusitis, asthma, mild systemic symptoms, etc.)

Chung SA, et al. *Arthritis Care Res (Hoboken).* 2021;73(8):1088-1105.

Assessing Disease Activity

Term	Definition
Remission	Lack of clinical signs/symptoms of AAV regardless of immunosuppressive therapy status
Refractory disease	Persistent active disease despite appropriate immunosuppressive therapy
Relapse	Reactivation of disease following a period of remission

Chung SA, et al. *Arthritis Care Res (Hoboken).* 2021;73(8):1088-1105.

Treatment Goals and Selection

Goals

- Rapid diagnosis and prompt treatment initiation

Induction phase (first 3 to 6 months)

- Mitigate inflammation → early remission → decrease renal scarring

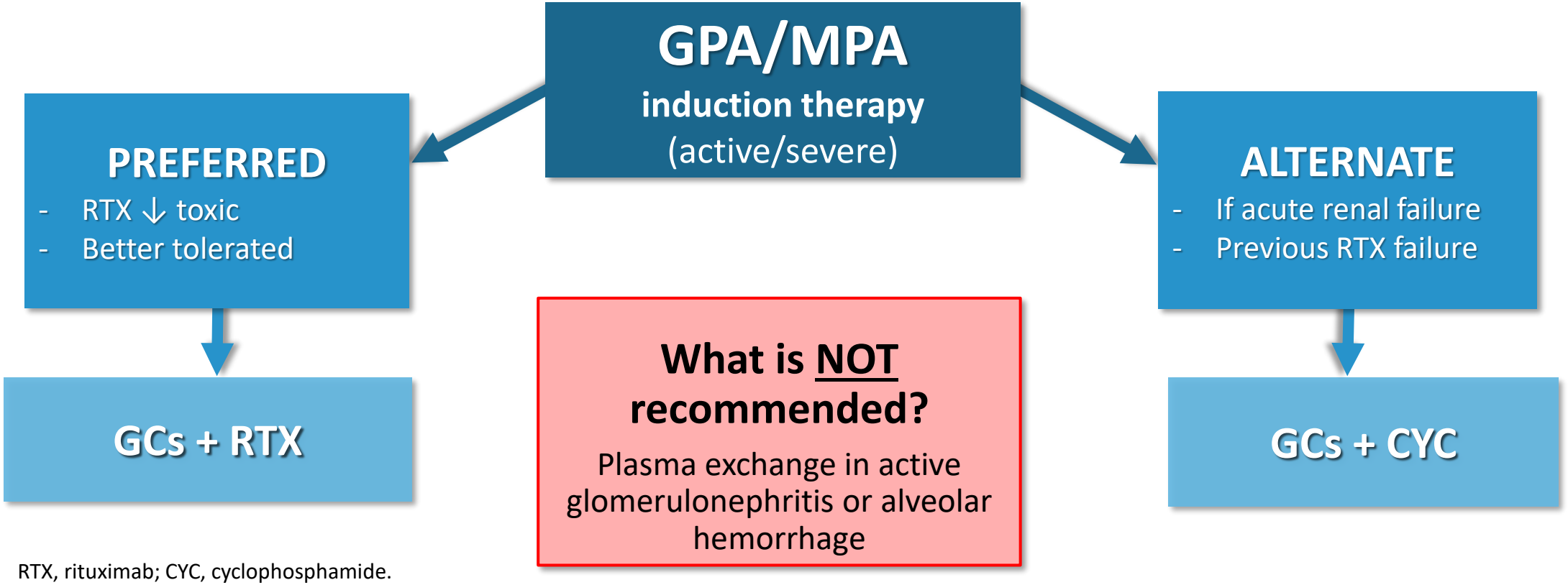
Maintenance phase (next ≥18 months)

- Preventing disease relapses, tapering glucocorticoids (GCs), and withdrawal of immunosuppressive therapy
- Limiting treatment-related toxicity

****Treatment is selected based on the subtype of AAV and disease activity****

Geetha D, Jefferson JA. *Am J Kidney Dis*. 2020;75(1):124-137.

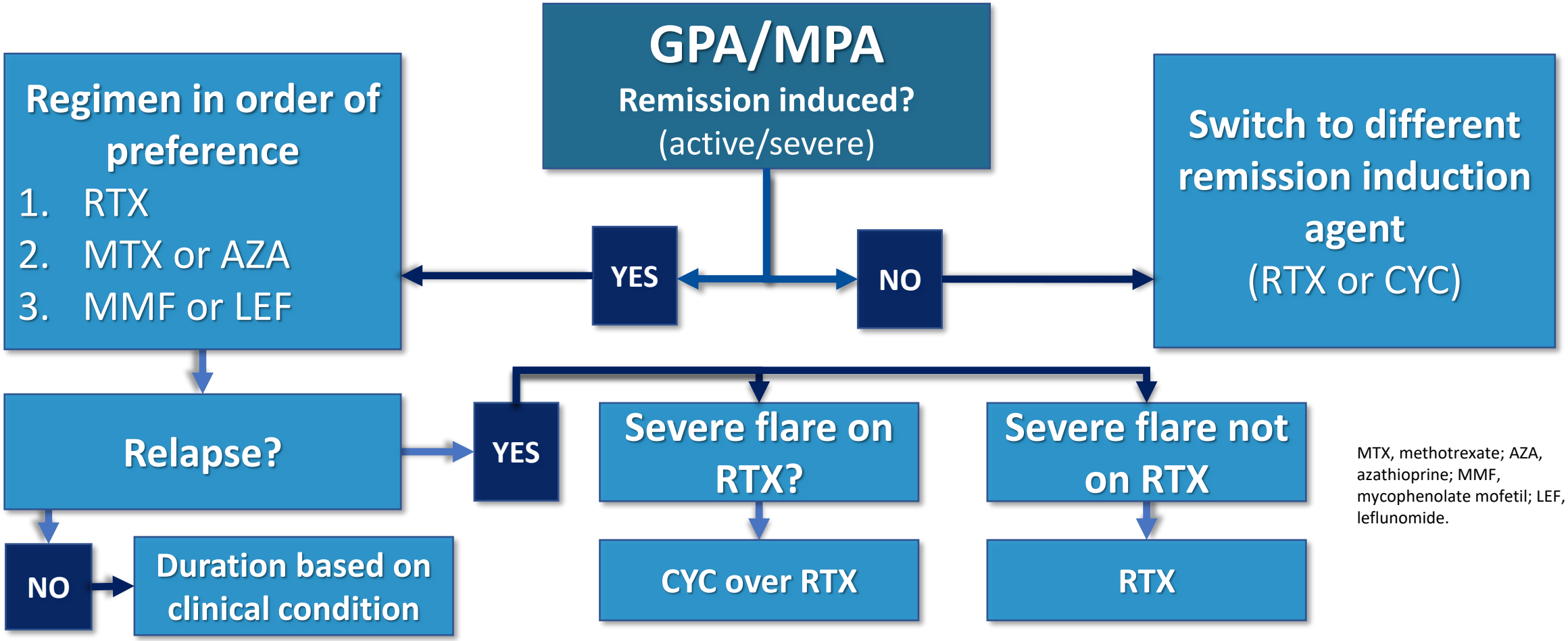
American College of Rheumatology: AAV Treatment Guidelines



RTX, rituximab; CYC, cyclophosphamide.

Chung SA, et al. *Arthritis Care Res (Hoboken).* 2021;73(8):1088-1105.

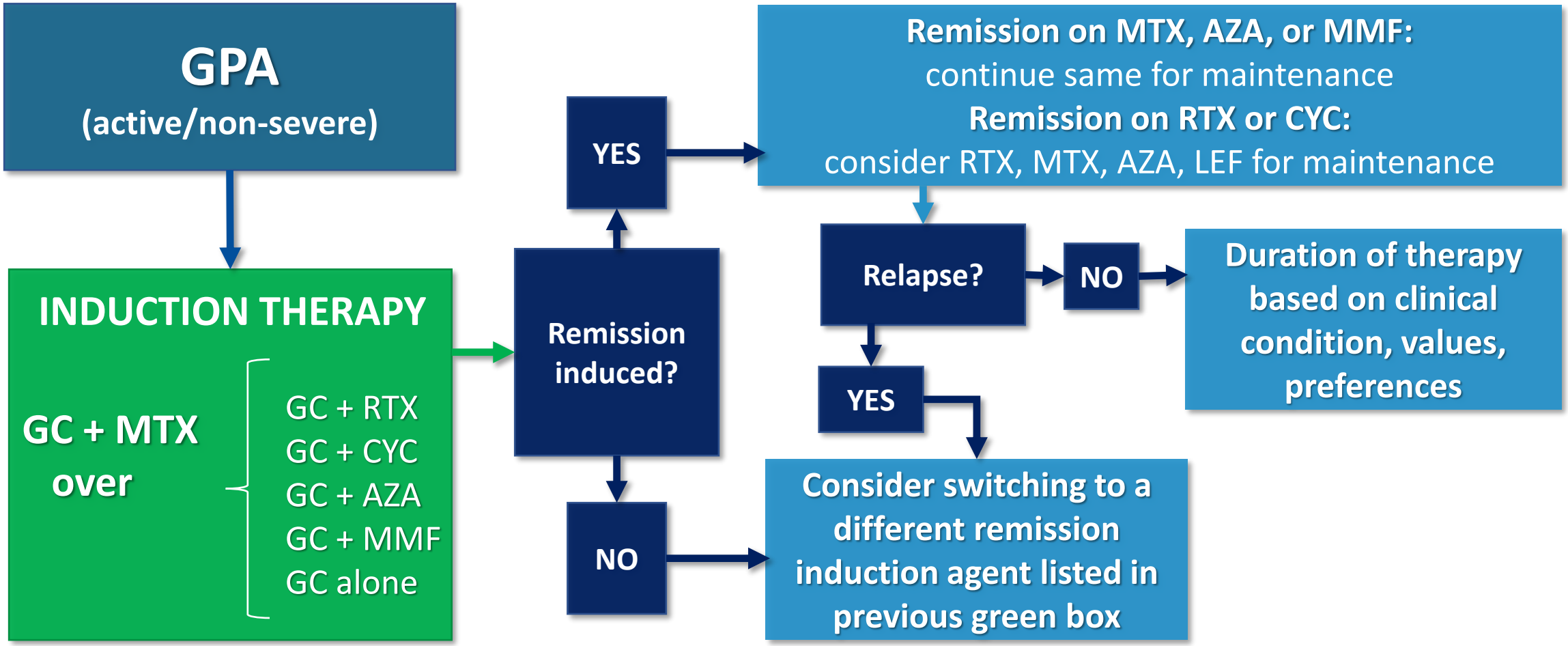
American College of Rheumatology: AAV Treatment Guidelines



MTX, methotrexate; AZA, azathioprine; MMF, mycophenolate mofetil; LEF, leflunomide.

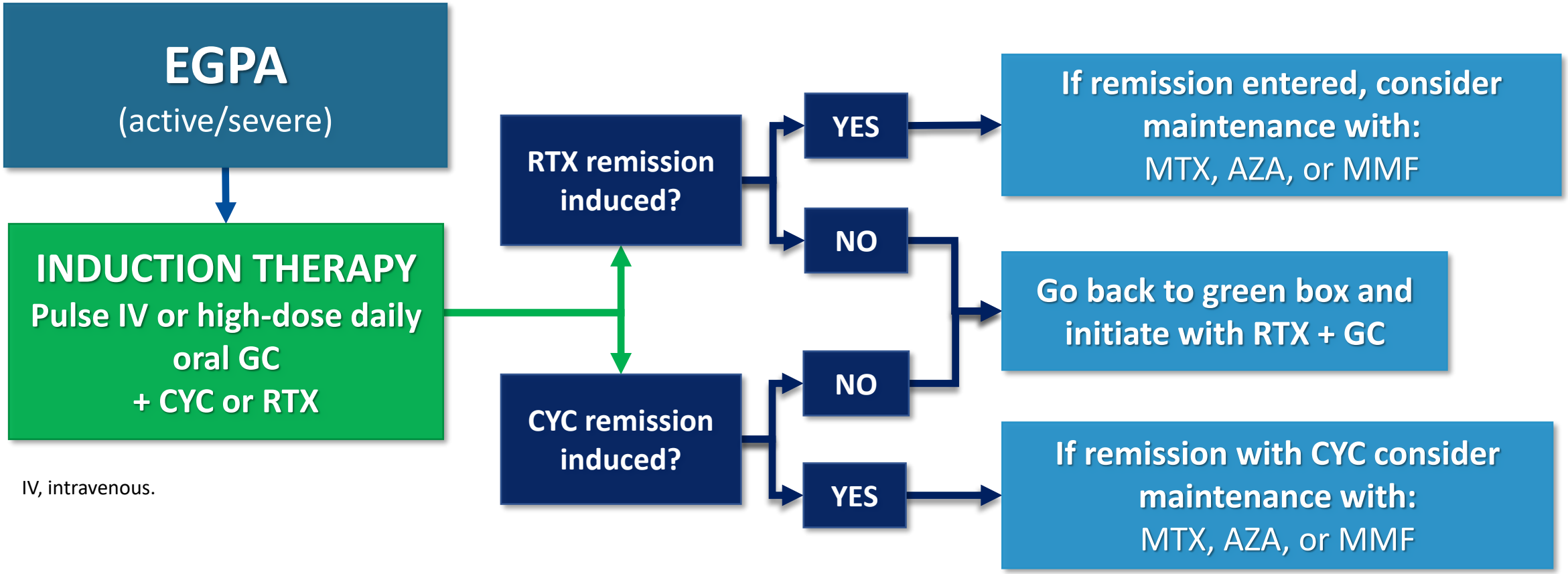
Chung SA, et al. *Arthritis Care Res (Hoboken).* 2021;73(8):1088-1105.

American College of Rheumatology : AAV Treatment Guidelines



Chung SA, et al. *Arthritis Care Res (Hoboken).* 2021;73(8):1088-1105.

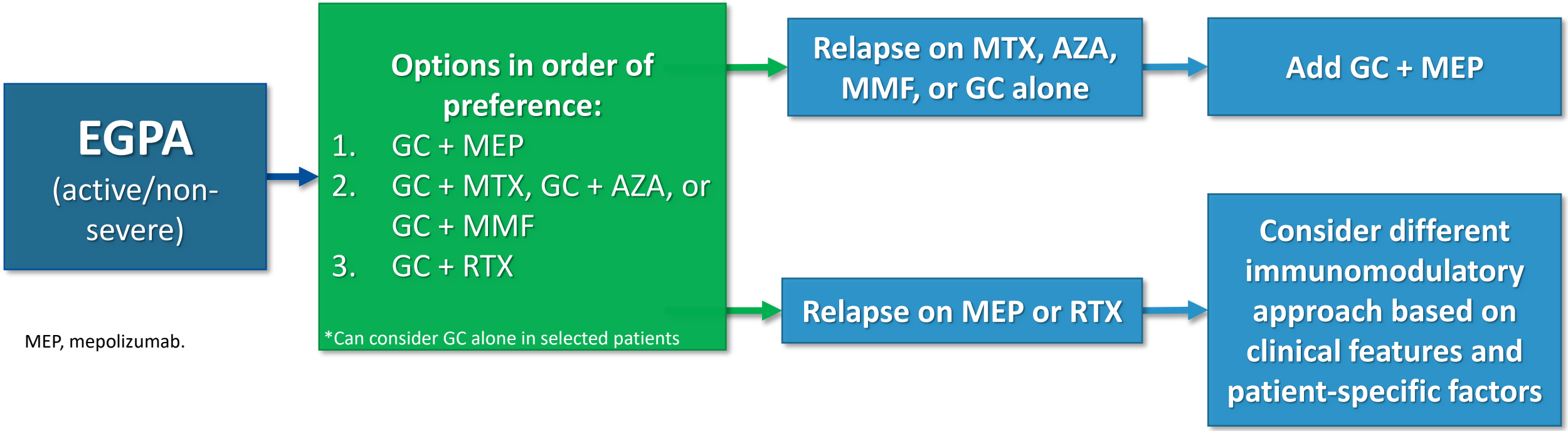
American College of Rheumatology : AAV Treatment Guidelines



IV, intravenous.

Chung SA, et al. *Arthritis Care Res (Hoboken).* 2021;73(8):1088-1105.

American College of Rheumatology : AAV Treatment Guidelines



MEP, mepolizumab.

Chung SA, et al. *Arthritis Care Res (Hoboken).* 2021;73(8):1088-1105.

Clinical Complications

Concerns with existing therapies

- Corticosteroids remain the cornerstone of therapy and are associated with significant adverse events
- Significant treatment associated toxicities result with repeat exposure in relapsing disease
- Significant risk for infection on immunosuppressive therapies
- Guideline recommendations are conditional due to the lack of high-quality trials

Impact on disease

- Applying current therapeutic regimens still result in disease relapse and permanent organ damage
- While advancement in treatments have significantly improved AAV prognosis, patients now suffer from treatment-related adverse events

Chung SA, et al. *Arthritis Care Res (Hoboken).* 2021;73(8):1088-1105.

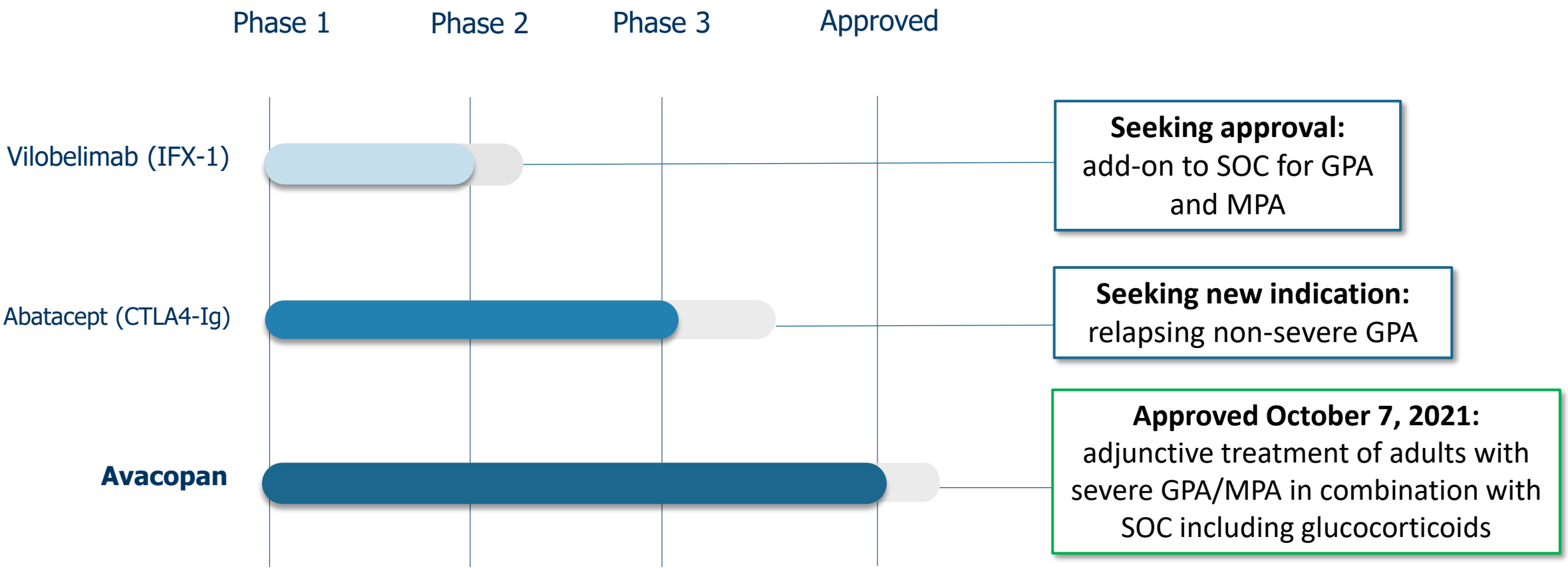
Treatment Gaps

Specific areas needing further investigation

- The need for more specific and reliable indicators of disease activity to guide treatment decisions
- Trials to clarify how best to use currently available medications (eg, dosing, duration, effective combinations, and in which population to use each medication)
- Trials to identify novel, targeted, and/or glucocorticoid-sparing agents with minimal toxicity
- Long-term studies to understand the course of disease and the safety of current therapies

Chung SA, et al. *Arthritis Care Res (Hoboken).* 2021;73(8):1088-1105.

New and Emerging Treatment Options



Abatacept for the treatment of relapsing, non-severe, granulomatosis with polyangiitis (Wegener's). ClinicalTrials.gov. ClinicalTrials.gov Identifier: NCT02108860 Updated April 14, 2021. Accessed February 10, 2022 .www.clinicaltrials.gov/ct2/show/record/NCT02108860; TAVNEOS. Prescribing information. ChemoCentryx, Inc; 2021; Safety and efficacy study of IFX-1 in add-on to standard of care in granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA). ClinicalTrials.gov. ClinicalTrials.gov Identifier: NCT03712345. Updated August 27, 2021. Accessed February 10, 2022. www.clinicaltrials.gov/ct2/show/record/NCT03712345?cond=ANCA-associated+Vasculitis&draw=3&rank=83

Newly Approved Therapy

Avacopan indication:

- Adjunctive treatment for adult patients with severe active AAV (GPA and MPA) in combination with standard of therapy including glucocorticoids.
- Avacopan does not eliminate glucocorticoid use.

Mechanism of action:

- Complement 5a receptor (C5aR) antagonist that inhibits the interaction between C5aR and the anaphylatoxin C5a.
- Avacopan blocks C5a-mediated neutrophil activation and migration.

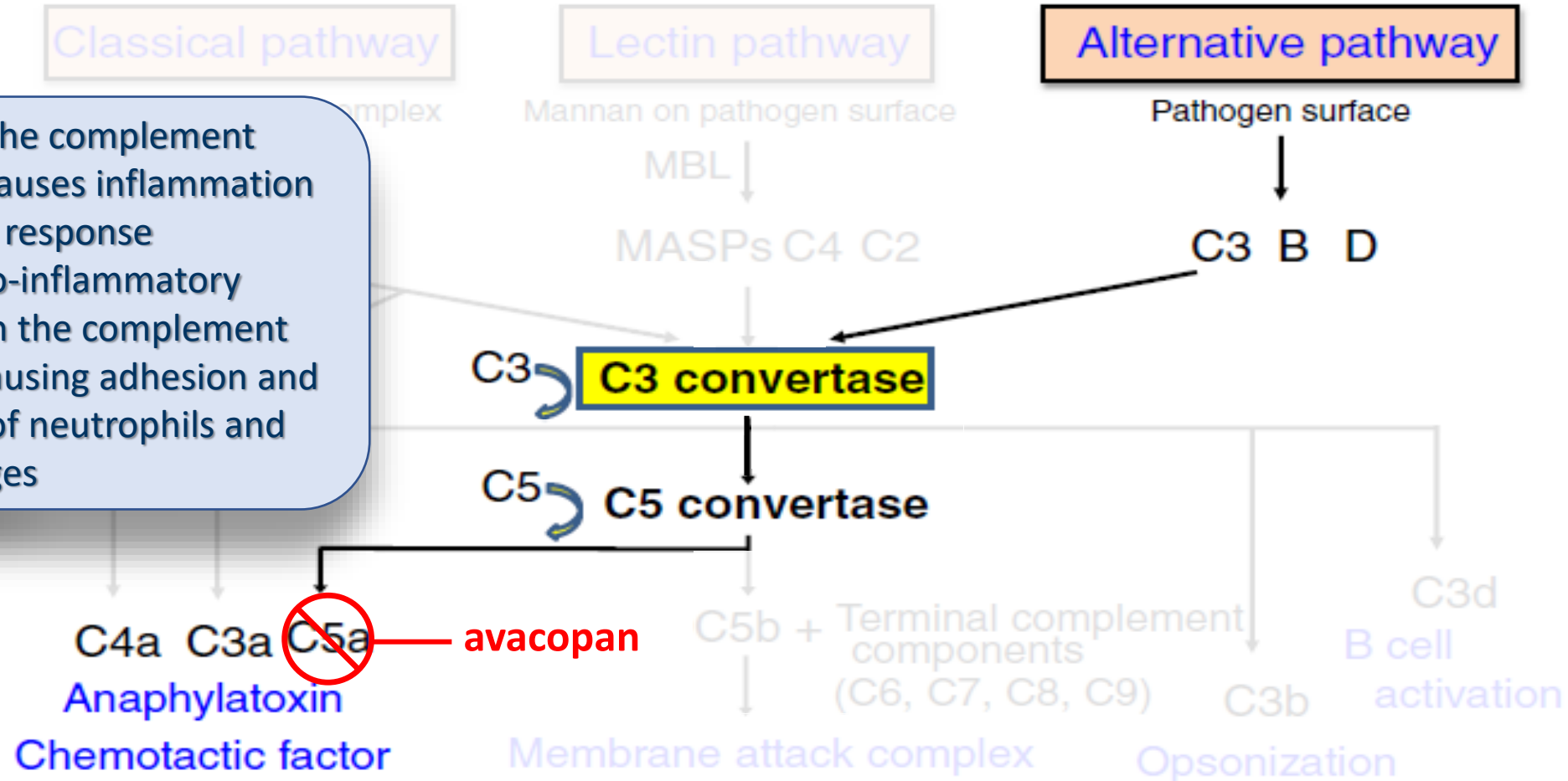
TAVNEOS. Prescribing information. ChemoCentryx, Inc; 2021.

Complement System

AAV

C5aR is part of the complement system, which causes inflammation and an immune response

- C5a is a pro-inflammatory mediator in the complement pathway causing adhesion and migration of neutrophils and macrophages



TAVNEOS. Prescribing information. ChemoCentryx, Inc; 2021; Republished from Horiuchi T, et al. *Inflamm Regener*. 2016; 36(11), under the terms of the Creative Commons Attribution 4.0 International License.

ADVOCATE Trial

Phase 3, randomized-controlled trial (n = 331)

- **Treatment group:** RTX or CYC + avacopan 30 mg orally twice a day (n = 166) + prednisone-matching placebo
- **Placebo group:** RTX or CYC + prednisone taper + avacopan-matching placebo

Primary end points

- Clinical remission at week 26 (BVAS of 0 and no receipt of glucocorticoids x4 weeks before week 26)
- Sustained remission (= remission at week 26 and week 52 and no receipt of glucocorticoids x4 weeks before week 52)

Jayne DRW, et al; ADVOCATE Study Group. *N Engl J Med*. 2021;384(7):599-609.

ADVOCATE Trial

	Avacopan 30 mg twice a day + placebo + CYC or RTX	Prednisone taper + placebo + CYC or RTX	P-value
Number of patients	166	164	
Remission at week 26	120 (72.3%)	115 (70.1%)	Noninferiority: *P* <0.001 Superiority: *P* = 0.24
Sustained remission at week 52	109 (65.7%)	90 (54.9%)	Noninferiority: P <0.001 Superiority: *P* = 0.007

Jayne DRW, et al; ADVOCATE Study Group. *N Engl J Med*. 2021;384(7):599-609.

Avacopan Counseling

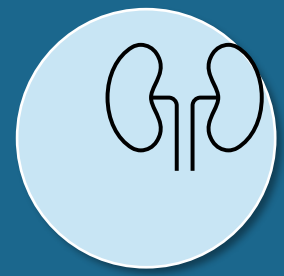
Nausea (24%)
Vomiting (15%)
Diarrhea (15%)
Upper abdominal pain (7%)

Headache (21%)
Dizziness (7%)
Paresthesia (5%)

Hypertension (18%)

Rash (11%)

Fatigue (10%)



Increase in serum creatinine (6%)

TAVNEOS. Prescribing information. ChemoCentryx, Inc; 2021.

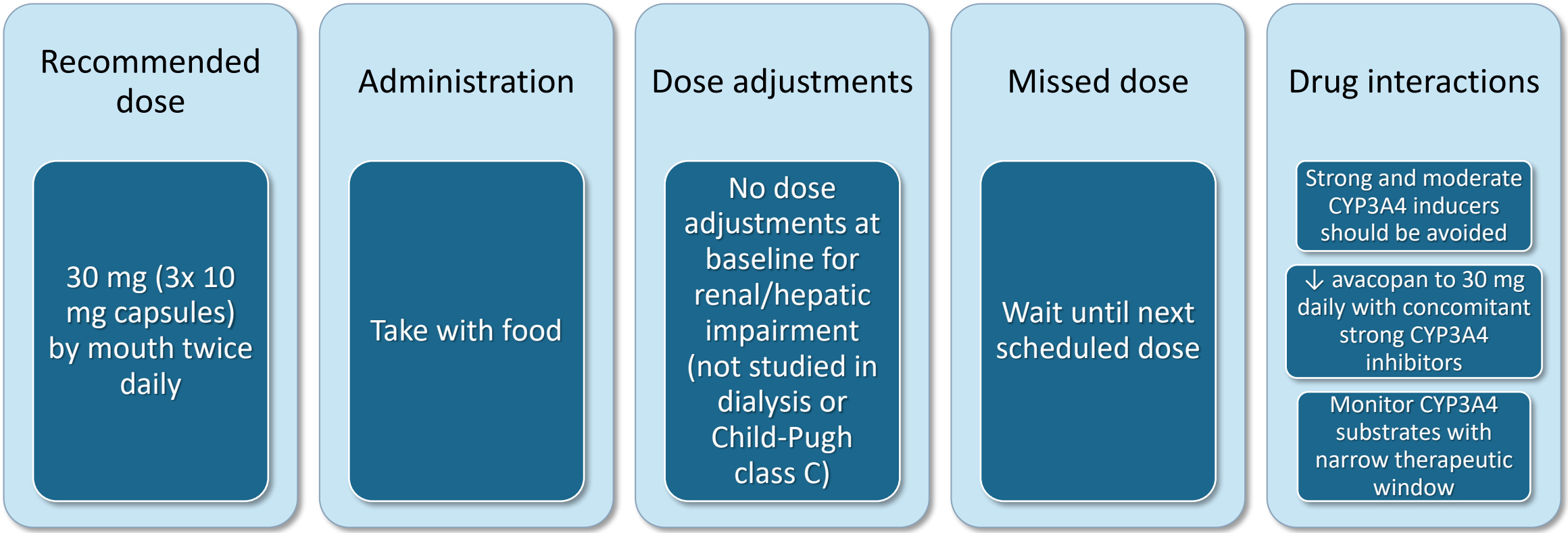
Avacopan Counseling

Warnings and precautions

- **Hypersensitivity reactions**
  - Angioedema
- **Hepatotoxicity**
  - Liver function test monitoring initially, every 4 weeks x6 months then as clinically indicated
- **Hepatitis B virus reactivation and life-threatening hepatitis B**
  - Screen for hepatitis B and consult specialist
- **Serious infection**
  - Pneumonia and urinary tract infection most common

TAVNEOS. Prescribing information. ChemoCentryx, Inc; 2021.

Avacopan Counseling



TAVNEOS. Prescribing information. ChemoCentryx, Inc; 2021.

Avacopan Counseling

Identify the plan for glucocorticoid dose

If glucocorticoid dose is to be reduced, educate patient on symptoms of withdrawal

- Anorexia, nausea, vomiting
- Fatigue, weakness, myalgias, abdominal pain
- Headache, fever, postural hypotension, tachycardia
- Emotional lability, delirium, psychotic states

*Avacopan is currently not intended to replace corticosteroids

Baker E. *Br J Clin Pharmacol*. 2021; TAVNEOS. Prescribing information. ChemoCentryx, Inc; 2021.

Key Considerations for Specialty Pharmacists

Abigail Jastrab, PharmD, BCPS

The Pharmacist's Role in AAV

Patient education and support

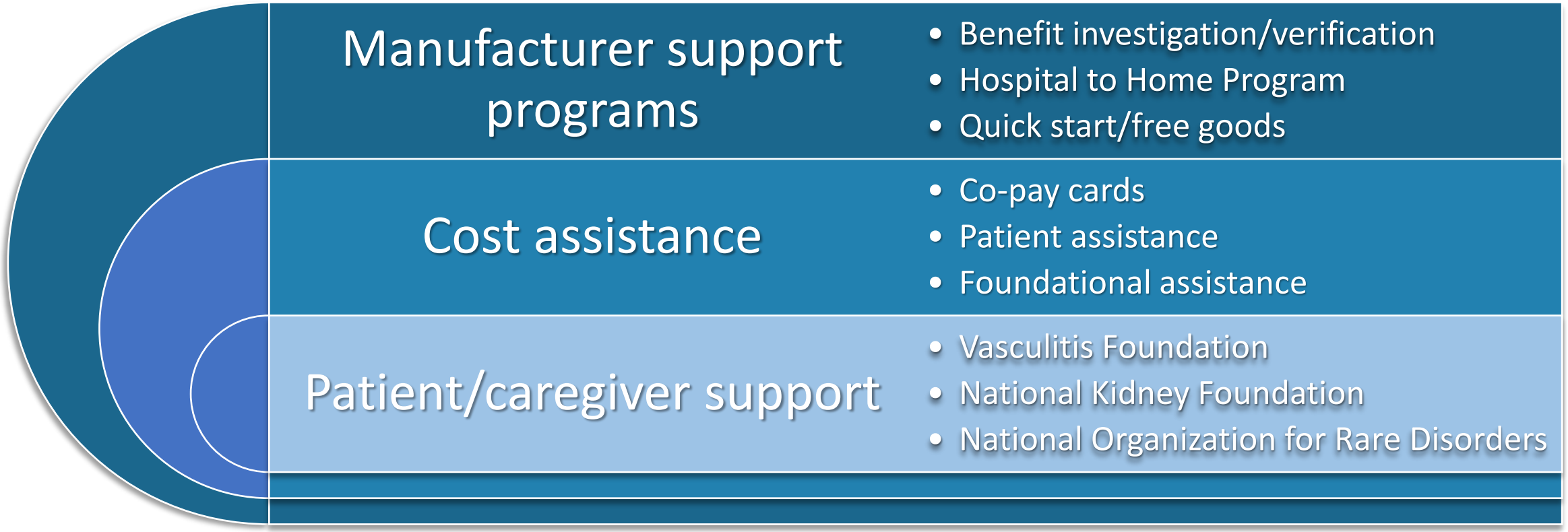
- 2014 study by Mooney et al. found patients with AAV consistently rank information related to treatment as either very or extremely important

- Chronic disease management
  - Adherence
  - Minimizing treatment-related toxicities
  - Collaboration with multidisciplinary team
  - Medication reconciliation

- Medication access
  - Financial
  - Payor coverage
  - Limited or exclusive distribution systems
  - Unique storage and shipping requirements

Mooney J, et al. *Rheumatology (Oxford).* 2014;53(8):1414-1421.

Patient Support Services



Chemocentryx. TAVNEOS connect. Accessed February 10, 2022. https://tavneos.com/support; Vasculitis Foundation. Accessed February 10, 2022. www.vasculitisfoundation.org; National Kidney Foundation. Accessed February 10, 2022. www.kidney.org; HealthWell Foundation. Accessed February 10, 2022. www.healthwellfoundation.org; National Organization for Rare Disorders. Accessed February 10, 2022. https://rarediseases.org

Conclusion

Bridging the Gap

- AAV is a complex disease that is difficult to diagnose and has significant disease burden and treatment-related toxicities
- Current treatment guidelines have several gaps present where appropriate pharmacologic recommendations can further improve patient outcomes
- Pharmacists have a key role in counseling patients, recommending appropriate novel therapies, and collaborating with the multidisciplinary team to improve patient outcomes

Additional Resources

Resources	
Vasculitis Foundation	www.vasculitisfoundation.org/
HealthWell Foundation: ANCA-Associated Vasculitis and Granulomatosis with Polyangiitis	www.healthwellfoundation.org/fund/anca-associated-vasculitis-wegeners-and-granulomatosis-with-polyangiitis/
National Organization for Rare Disorders	https://rarediseases.org/
National Kidney Foundation	www.kidney.org/

Posttest Questions

Posttest Question 1

Which of the following is true regarding antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV)?

A. A positive ANCA test is conclusive for an AAV diagnosis
B. The risk of relapse is 30% to 50% over 5 years with treatment
C. Acute renal injury is a common clinical presentation for all AAV subtypes
D. Purpura and weight gain have the largest negative impact on quality of life

Posttest Question 2

SM is a 55-year-old man with severe active granulomatosis with polyangiitis. SM struggles with uncontrolled hypertension, hyperglycemia, and other symptoms deemed related to his high prednisone doses. His physician recently tapered his prednisone to gain better control of SM's symptoms, but the taper resulted in this current flare. SM's physician is restarting induction therapy with rituximab (previous induction therapy with cyclophosphamide) and prednisone 60 mg orally daily. The pharmacist is asked to optimize his regimen to be able to reduce his prednisone dose.

A. Change rituximab to cyclophosphamide
B. Retry the steroid taper
C. Add avacopan
D. Add methotrexate

Posttest Question 3

JC is newly diagnosed with microscopic polyangiitis AAV, and the pharmacist is filling her first prescription for avacopan. Which counseling point should the pharmacist cover with JC, as it pertains to avacopan?

A. Signs and symptoms of stroke

B. Infertility

C. Significant drug interaction with prednisone

D. Signs and symptoms of hypersensitivity

Posttest Question 4

After participating in this activity, how confident are you with new treatment options for AAV?

A. Not at all
B. Somewhat
C. Moderately
D. Very
E. Extremely

Question and Answer Session

Thank you!